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Altered thalamic response to levodopa in Parkinson's patients with dopa-induced dyskinesias

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ABSTRACT **Parkinson's disease (PD) is a progressive neurologic condition characterized by tremor, slowness, stiffness, and unstable posture. Degeneration of dopamine-producing neurons in the substantia nigra causes PD. Treatment with levodopa, a precursor of dopamine, initially ameliorates the clinical manifestations of PD. However, chronic levodopa treatment can produce severe involuntary movements (so-called dopa-induced dyskinesias or DID), limiting treatment. Pallidotomy, placement of a surgical lesion in the internal segment of the globus pallidus, reduces DID. Because this result is inconsistent with current theories of both basal ganglia function and DID, it prompted us to investigate the brain's response to levodopa. We measured regional cerebral blood flow response to levodopa with positron-emission tomography in 6 PD patients with DID, 10 chronically treated PD patients without DID, 17 dopa-naïve PD patients, and 11 normals. The dose of levodopa was chosen to produce clinical benefit without inducing DID. This strategy allowed us to examine the brain response to levodopa across groups without the confounding effect of differences in motor behavior. We found that the DID group had a significantly greater response in ventrolateral thalamus than the other groups. This was associated with decreased activity in primary motor cortex. These findings are consistent with increased inhibitory output from the internal segment of the globus pallidus to thalamus after levodopa administration. They provide a physiological explanation for the clinical efficacy of pallidotomy and new insights into the physiology of the basal ganglia.**

Parkinson's disease (PD), a disease of brain dopamine deficiency, results from the degeneration of nigrostriatal neurons (1). Levodopa, the immediate precursor of dopamine, is the primary treatment for PD. Initially, treatment with levodopa ameliorates the clinical manifestations of PD such as slowness or reduction of spontaneous movement (bradykinesia or akinesia), tremor, rigidity, and an unstable posture (2). Many patients, however, develop a debilitating side effect of chronic levodopa treatment, consisting of drug-induced involuntary movements (dopa-induced dyskinesias, or DID). The development of DID severely limits effective treatment with levodopa.

Recent studies have shown that pallidotomy surgery, the placement of an electrolytic lesion in the internal segment of the globus pallidus (GPi), consistently decreases DID (3). Thus, the presence and severity of DID have become important selection criteria for patients undergoing pallidotomy (3). However, it is puzzling that pallidotomy's favorable effect on DID is inconsistent with current theories of basal ganglia function used to explain the mechanism of DID (4).

The output of the basal ganglia is through the GPi. GPi, in turn, sends projection neurons to thalamus thought to tonically inhibit thalamocortical circuits, including those involved in motor activity. Currently, some investigators believe that levodopa causes underactivity of GPi neurons thereby releasing the inhibition of thalamocortical motor circuits, which leads to the production of involuntary movement in patients with DID (5). According to the commonly accepted model of basal ganglia function, pallidotomy would reduce the inhibitory output of the GPi even further, potentially increasing, rather than decreasing DID. This contradiction challenges our understanding of basal ganglia physiology and the pathophysiology of DID (4). Therefore, determining the neurophysiological abnormalities underlying DID may provide new understanding of basal ganglia function, as well as enhance our understanding of pallidotomy surgery.

The present study addresses the question of how blood flow responses to an acute dose of levodopa differ between PD patients who have developed DID and those who have not. Changes in regional cerebral blood flow are thought to reflect neuronal activity, primarily in axonal terminal fields (6). Positron emission tomography (PET) permits the *in vivo* assessment of regional cerebral blood flow responses to pharmacologic challenges (7–15) and thus is a useful method for investigating DID. Because DID occur in response to levodopa, we chose to assess neurophysiological responses to an acute dose of levodopa.

MATERIALS AND METHODS

Subjects. *PD patients.* Patients with clinically diagnosed idiopathic PD (16) were recruited primarily from the Movement Disorders Center at Washington University School of Medicine. Patients were excluded for any evidence of secondary parkinsonism (e.g., drug-induced or atypical presentation), dementia (Mini-Mental Status Exam score <26) (17), depression (Hamilton Depression Scale score > 10) (18), history of other neurological disorders, psychiatric disorders, substance abuse, neuroleptic use, or suspicion of pregnancy. All of the patients were right-handed (19) and 21 were male and 12 were female. Three groups of patients were specifically recruited: patients with no history of levodopa or other dopamine agonist treatment (dopa-naïve, $n = 17$), patients on chronic levodopa treatment but without DID ($n = 10$) and patients on chronic levodopa treatment with DID ($n = 7$). All of the patients had typical features of clinically defined PD, including patients who had not developed DID. Approximately 70% of patients remain DID-free after several years of treatment (20).

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Abbreviations: PD, Parkinson's disease; DID, dopa-induced dyskinesias; PET, positron-emission tomography; GPi, internal segment of the globus pallidus; SNpr, substantia nigra, pars reticulata; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale.

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One DID patient was excluded from analysis because he had dyskinesias during his post-levodopa scans. This strategy allowed us to look at the physiological response to levodopa *without* the confounding effect of differences in motor behavior.

Twenty-one (64%) of our 33 PD patients had greater motor symptoms on the right side of the body, whereas only 12 (36%) had greater motor symptoms on the left side of the body. In addition, within the DID group, five of six patients had greater motor and DID symptoms on the right side of the body. Eight dopa-naïve PD patients had unilateral motor symptoms; the remaining patients had bilateral motor symptoms. See Table 1 for additional information.

Normals. Eleven right-handed women and three right-handed men without PD were recruited by using the same exclusionary criteria as outlined above. One woman and two men were excluded from analysis because their plasma levodopa levels were extremely low (average post-levodopa plasma levels <400 ng/ml), suggesting poor enteral absorption of the drug. See Table 1 for additional information.

Written informed consent was obtained from all subjects before their participation in the study. The study protocol was approved by the Radioactive Drug Research Committee and the Human Studies Committee of Washington University School of Medicine.

Protocol. All PD patients on levodopa therapy refrained from taking levodopa for at least 12 hr before participation in the PET protocol. At the beginning of the study, all subjects took carbidopa 200 mg orally and had a baseline clinical evaluation consisting of the Unified Parkinson's Disease rating scale (UPDRS) (21) and the modified Hoehn & Yahr rating scale (16). They then were placed in the scanner, a 20-gauge catheter was inserted into an arm vein to permit injection of $H_2{}^{15}O$, and in some subjects a similar catheter was inserted into the radial artery at the wrist after local lidocaine anesthesia for arterial blood sampling. An individually molded polyform mask helped stabilize each subject's head within the scanner. Radio-opaque markers placed in the external auditory canals and a lateral skull radiograph with the center PET slice indicated by a radio-opaque wire provided a record of the subjects' exact head position in relation to the PET (22).

Next, baseline blood samples were taken, and two to three baseline 40-sec PET measurements of blood flow (23) were obtained 15 min apart, as described below. Levodopa/carbidopa then was given orally (150 mg/37.5 mg). We chose a dose of levodopa that was generally lower than the DID patients' usual doses, and thus was unlikely to induce dyskinesias. Patients were observed for movements by at least one movement disorders specialist during each scan. One DID patient was excluded from analysis due to dyskinesias during the scans. This strategy allowed us to look at the physiological response to levodopa across groups without the confounding additional effect of a difference in motor behavior during the scans between groups. Approximately 45–75 min after levodopa, two to three additional blood flow measurements were obtained. Clinical ratings (modified motor UPDRS including ratings for tremor, rigidity, bradykinesia, and tapping speed for upper extremities; 16 total possible points) and blood samples were obtained at the time of each scan and every 15 min after administration of levodopa. During each PET scan, the room was darkened and subjects' eyes were closed.

PET Methods. All PET studies were performed on a Siemens 953B scanner (CTI, Knoxville, TN) in 2-dimensional mode. Data were recorded simultaneously for 31 slices with a center-to-center slice separation of 3.4 mm (24). After subjects were positioned, a transmission scan used for individual attenuation correction was acquired with rotating rod sources containing $^{68}Ge/^{68}Ga$. PET images were reconstructed with a transverse resolution of 14 mm full width half maximum. Blood flow was measured by using a 40-sec emission scan after the i.v. bolus injection of 5–10 ml of saline containing 40–50 mCi (1 Ci = 37 GBq) of ^{15}O-labeled water (23, 25, 26).

Levodopa Measurements. Levodopa and carbidopa levels were measured by using HPLC with electrochemical detection following a modified version of published methods (27, 28). We added an internal standard, 3,4-dihydrobenzylamine (DHBA), to simplify quantification. Although our primary interest was in levodopa, in the course of developing the method we found that it was possible to simultaneously measure carbidopa as well.

PET Data Analysis. To minimize artifact from movement between scans, PET images for each subject first were aligned to a baseline scan from that subject's scan series by using an automated method (29). All scans then were placed into Talairach atlas space (30). We analyzed all regional data by using normalized PET counts, which are linearly related to quantitative regional cerebral blood flow (31).

The data analysis strategy was designed to determine which regional brain responses to levodopa differentiate DID from non-DID patients. This strategy also was designed to minimize Type 1, or false positive errors, to ensure that each finding is reliable (32, 33). Thus, our strategy may not detect other lower-level responses.

We first determined which regions were reliably affected by levodopa activation in DID and non-DID patients. For each group, we randomly selected one pre-levodopa scan and one post-levodopa scan from each subject in that group and subtracted the pre- from the post-levodopa scan. We then created a composite subtraction image for each group averaging the subtraction pairs from each group. The composite subtraction images from the two groups were used to generate hypotheses about which regions of the brain responded to levodopa.

We used an automatic search routine (34) to identify peak responses in these two composite hypothesis-generating subtraction images. Candidate regions were selected from this

Table 1. Demographic and clinical variables: mean (SD)

	Parkinson's disease groups			
	Normals	Dopa-naive	Dopa-treated with no dyskinesias	Dopa-treated with DID
n	11	17	10	6
Age	53.6 (14.4)	60.9 (14.2)	69.9 (3.2)*	60.3 (8.0)
Hamilton depression scale	1.5 (1.6)	2.6 (2.5)	1.1 (2.8)	2.5 (3.1)
Mini-mental status score	29.6 (0.7)	28.8 (1.9)	28.7 (1.3)	28.7 (2.3)
Hoehn and Yahr stage		1.7 (0.3)	2.6 (0.6)†	2.4 (0.8)†
Symptom duration, years		2.8 (2.9)	7.6 (6.4)	10.8 (6.5)†
Modified UPDRS change		−2.7 (2.2)	−3.6 (3.3)	−3.0 (3.4)
Treatment duration, years			5.9 (5.7)	7.8 (6.8)

*Significantly different from normals ($P < 0.05$).
†Significantly different from dopa-naive group ($P < 0.05$).

peak-search if they (*i*) had >8% change in magnitude and (*ii*) had relevance to dopaminergic pathways. For the non-DID group, we selected three regions and for the DID group, we selected five regions. Once these candidate regions were selected for each group, the paired scans used to create these images were discarded. We then tested the statistical significance of the candidate responses by using the remaining scans in each group. To determine this, a 10-mm diameter sphere-shaped volume of interest was centered on the coordinates of the candidate regions in the remaining pre- and post-levodopa scans. This size was chosen to best approximate the search volume used in the peak identification routine and to reduce partial volume contributions from nearby regions.

The candidate regions selected from the hypothesis-generating image from non-DID patients were examined in the remaining scans from these patients and the normal subjects. Mean changes in blood flow were calculated for each of these candidate regions in the remaining scans. One-tailed *t* tests were conducted on the mean changes in blood flow. Critical *P* values were Bonferroni-corrected to minimize type I error. If a candidate region reached significance, it was accepted as a reliably activated region for the group.

The candidate regions selected from the hypothesis-generating image from DID patients were examined in the remaining scans from the DID patients and tested for statistical significance precisely as done for the non-DID patients.

To determine how DID and non-DID patients differed in their response to levodopa, we took the reliably activated regions from the above analysis and examined them for differences across groups. These regions were applied to all groups, using all scans to generate mean pre- and post-levodopa values for each subject.

The mean blood flow values for each region were analyzed by using repeated measures general linear models with group as the between-subjects variable and drug (pre- vs. post-levodopa) as the repeated variable. These analyses were performed to determine whether there were any significant interactions between group and drug, indicating that groups responded to levodopa differently. We particularly were interested in whether the DID patients responded to levodopa differently compared with non-DID patients in any region. Appropriate post-hoc comparisons were used to examine any significant main effects or interactions in more detail. In addition, correlations were performed between relevant clinical variables, plasma levodopa levels, and blood flow responses.

RESULTS

Peak Identification. In the non-DID group's composite subtraction image, only three regions of increased blood flow were found: The left putamen (−23, −5, 6), midbrain (stereotactic coordinates: −1 mm, −31 mm, −4 mm), and right amygdala (13, −5, −16). No regions with decreased blood flow were found. The statistical significance of these three candidate regions of increased blood flow was confirmed in the remaining scans for the non-DID patients (*t* tests, *P*s < 0.01; see Table 2).

Table 2. Levodopa-induced mean percent change (SD) in blood flow in hypothesis testing data sets

	% Change	*t* Value	*P* value
Left putamen	4.6 (10.3)	3.33	0.001*
Midbrain	8.7 (13.1)	4.88	<0.001*
Right amygdala	4.6 (13.2)	2.56	<0.01*
Left thalamus	18.9 (18.2)	2.76	0.017†
Left hippocampus	10.5 (9.8)	3.03	<0.01†

*Regions generated and tested in subjects without DID.
†Regions generated and tested in PD patients with DID.

From the DID group's composite subtraction image, we chose four candidate regions of increased blood flow in the left ventrolateral thalamus (stereotactic coordinates: −13 mm, −15 mm, 2 mm), left putamen (−25, 1, 10), right globus pallidus (25, −17, 2), and left hippocampus (−27, −25, −8). The left thalamic response had the highest magnitude change (13.9%) of all regions identified by the peak identification program. We chose only one candidate region, the right thalamus (13, −23, 8), with reduced blood flow. Of these five candidate regions (four increases and one decrease), the left thalamus (see Fig. 1) replicated at a borderline level (*t* test, $P = 0.017$; critical $P = 0.01$) and the left hippocampus significantly replicated (*t* test, $P < .01$).

Group Comparisons. To determine differences among groups, all regions found to be reliably activated in the hypothesis-testing step for either group were examined. These regions were the three regions from the non-DID group (left putamen, midbrain, and right amygdala) and the two regions from the DID group (left thalamus and left hippocampus). Each region was analyzed with a repeated measures general linear model, with drug (pre- vs. post-levodopa flow) as the repeated measure and group (normals, dopa-naïve, dopa-treated, and DID) as the between-subjects variable. Results from these five repeated measures analyses revealed the following:

1. Most importantly, there was a significant interaction between group and drug for the left thalamus region only [$F(3, 39) = 4.17$, $P = 0.01$]. Post-hoc comparisons revealed that DID patients had a significantly greater increase in blood flow in this region compared with all other groups (see Fig. 2). Thus, the magnitude of the blood flow response to levodopa in the left thalamus statistically distinguished DID patients from all other groups. We explored the asymmetry of the thalamic response by comparing the left thalamic response with the response in the right thalamus (mirror image of the left thalamic volume of interest) by using paired *t* tests for each group of subjects. A significant difference was found for the

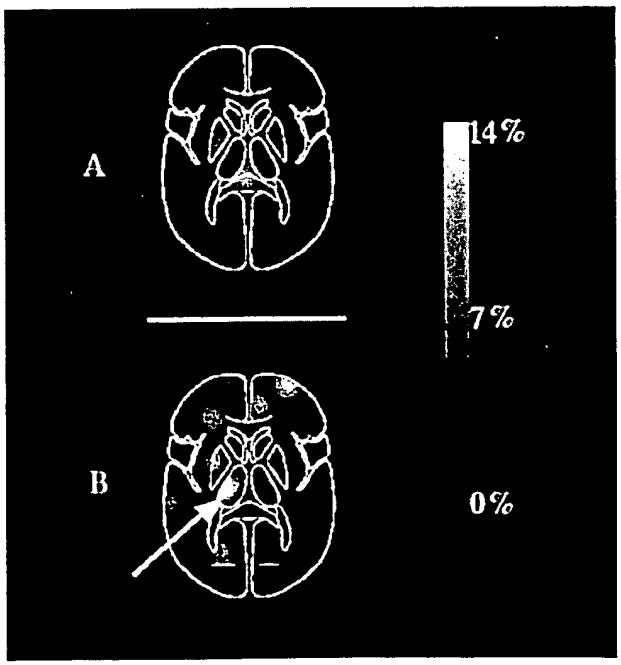

FIG. 1. Composite subtraction PET images (post-levodopa scans minus pre-levodopa scans) shown in transverse orientation, Talairach z level = 6. (*A*) PD patients without DID ($n = 26$). (*B*) PD patients with DID ($n = 6$). Arrow indicates significant thalamic response in this group.

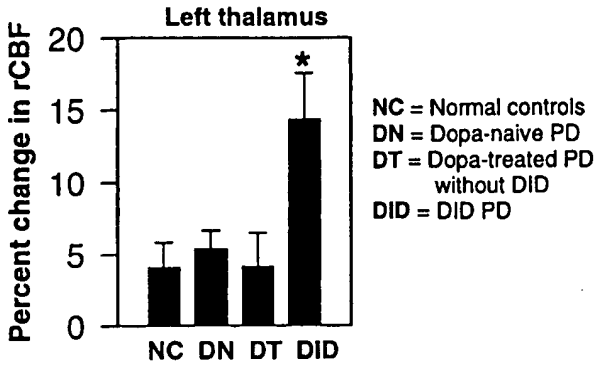

FIG. 2. Mean (± SEM) change in blood flow after levodopa administration for the left thalamus in each group. A group × drug interaction was found only for the left thalamus activation (see *Results* for details). *, Significantly greater increase in blood flow compared with all other groups.

DID group only (left = 14% increase, right = 4% increase, P = 0.04, two-tailed).

2. Main effects of drug were found for all 5 regions (Ps <0.01), indicating significantly increased blood flow after levodopa administration, collapsing across groups, in all regions.

3. There were no main effects of group on overall flow for any region, indicating that there were no systematic differences between groups, collapsing across condition (pre- and post-levodopa), in these regions.

Relationship Between Clinical Variables and Regional Responses. There were no significant correlations between regional blood flow changes in PD patients and symptom duration or change in UPDRS scores after levodopa administration. To examine the effect of symptom and treatment duration on the thalamic response in the PD subgroups more stringently, we included these variables as covariates in repeated measures general linear analyses. The results demonstrated that the interaction between drug (pre- vs. post-levodopa) and PD group for the left thalamic response was still significant (Ps <0.05). Thus, differences between PD subgroups in duration of symptoms or duration of dopa-treatment could not explain differences between PD subgroups in the thalamic response to levodopa.

Clinical Response and Levodopa and Carbidopa Plasma Levels. Levodopa and carbidopa plasma concentrations were measured in 34 subjects. Mean levodopa concentrations peaked between 30 and 60 min after taking levodopa and then remained above levels found to provide symptomatic benefit in other studies (35) during the post-levodopa scans. PD patients demonstrated significant clinical improvement after levodopa administration at the time of the post-levodopa scans, as measured by the modified UPDRS scale (t test, $P < 0.001$), providing further evidence of the therapeutic efficacy of these levodopa levels in our sample. Carbidopa concentrations remained stable across the study. There was no overall effect of group on levodopa levels (P = 0.15).

Relationship Between Levodopa Plasma Levels and Regional Responses. Pearson correlation coefficients were calculated between the five regional responses and levodopa plasma levels at the time of the post-levodopa scans for all subjects. These correlations were not significant.

Global Blood Flow. Although we analyzed all regional data by using normalized PET counts, which are linearly related to quantitative regional cerebral blood flow (31), we also quantified absolute global blood flow in 25 subjects. Global blood flow values did not change significantly after levodopa administration (pre-levodopa mean flow = 59.6 ml/min × 100 g, SD = 15.3; post-levodopa mean flow = 57.6 ml/min × 100 g, SD = 12.8; paired t test, P = 0.24), consistent with other published reports (36, 37).

DISCUSSION

We found that DID patients had large responses in the left thalamus after a dose of levodopa, distinguishing them from all other groups. Responses in the other regions examined did not discriminate DID patients from other PD patients or normals. The striking difference in thalamic response between DID patients and all other groups may represent a significant abnormality in the neurophysiological response of the basal ganglia-thalamocortical circuit to levodopa in patients with DID. We hypothesize that, in DID patients, levodopa causes the inhibitory output of GPi neurons to increase, causing increased flow in the thalamus over the axon termini of GPi neurons (6, 38).

The thalamic response in the DID patients was centered between the left ventroposterolateral and ventrolateral nuclei but likely also involves neighboring nuclei. The GPi and the substantia nigra, pars reticulata (SNpr) have major γ-aminobutyric acid projections to the ventrolateral and ventral anterior nuclei, which in turn provide glutamatergic input to motor, premotor, supplementary motor, and prefrontal cortex (4). The asymmetry of this thalamic response in DID may reflect greater PD manifestations and dyskinesias on the right side of the body in five of the six patients, although all had some bilateral symptoms. The sixth patient had relatively symmetrical involvement at baseline clinical evaluation and was not different from the other patients in the degree of thalamic response to levodopa. Thus, the left lateralization of the thalamic response may indicate, at least in part, the lateralization of symptoms.

Our results and interpretation contradict the common notion that levodopa reduces inhibitory output from GPi to thalamus, leading to increased excitatory output from thalamus to cortex, producing involuntary movements in patients with DID (5). Two types of animal studies support the prevailing model. First, a lesion in the subthalamic nucleus (STN) causes involuntary movements such as hemiballismus and chorea. A STN lesion also causes reduced activity of GPi/SNpr neurons, suggesting that targets of GPi/SNpr neurons, such as thalamus, may have reduced inhibitory input, triggering involuntary movements (39). Second, monkeys with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism that have developed DID after chronic levodopa treatment have abnormally high glucose uptake in STN. The increased glucose uptake in STN could reflect increased inhibitory input from the external segment of the globus pallidus, which would subsequently reduce its excitatory input to GPi/SNpr (40). Thus, GPi/SNpr neurons may have reduced activity, and consequently reduce their inhibitory action on thalamus, producing dyskinesias. However, in this study (40), glucose uptake was measured while these animals were actively dyskinetic; and feedback from the movements could confound interpretation of the results. Specifically, increased glucose uptake in STN also could reflect increased excitatory input directly from cortex to STN, which might be expected to occur during movements (41).

There are some inconsistencies with this model. This model predicts that pallidotomy would increase DID; whereas, widespread clinical observations demonstrate that pallidotomy consistently reduces DID. If this commonly accepted model were correct, we would have expected a larger decrease in thalamic blood flow in the DID patients compared with non-DID patients after levodopa administration. In addition, Matsumura *et al.* (42) reported that in monkeys who were made dyskinetic by injection of the γ-aminobutyric acid antagonist bicuculline into the external segment of the globus pallidus, neuronal firing increased in many GPi neurons just

before the onset of dyskinesias. They also found an abnormal pattern of firing characterized by bursts and pauses in the external segment of the globus pallidus and GPi neurons after injection. These changes in GPi firing associated with dyskinesias are not consistent with the current models. On the other hand, Hutchison *et al.* (43) reported that the average firing rate in GPi neurons decreased after s.c. apomorphine administration in PD patients undergoing pallidotomy surgery; some of whom experienced dyskinesias. However, no direct comparisons were performed between patients with and without DID. In addition, no changes in firing patterns were reported. Therefore, it is unclear from that study whether GPi neurons increase or decrease firing in response to dopamine agonists.

Two possible mechanisms could explain our finding of increased thalamic blood flow in DID patients after levodopa administration: (*i*) increased inhibitory input from GPi to thalamus or (*ii*) increased excitatory input from cortex to thalamus. To distinguish between these possibilities, we performed an exploratory analysis of our data examining the effect of levodopa on blood flow in motor cortex. If there were increased inhibitory input to thalamus, then thalamic output to motor cortex would be reduced and blood flow there also would be reduced. If there were increased excitatory input from cortex to thalamus, then flow in the motor cortex would be either increased or unchanged. Our images adequately sampled the arm/hand of motor cortex as defined by coordinates from a previous PET study (44). Left and right motor cortex regions were analyzed as previously described for other regions. DID subjects had a significant decrease in left primary motor cortex blood flow, whereas the rest of the groups had either increases in flow (dopa-naïve PD patients, normals) or no change (dopa-treated PD patients without DID). No significant change was found in the right motor cortex for any of these groups (see Fig. 3). These results are internally consistent with the interpretation that the significantly increased thalamic blood flow found in DID subjects is related to increased inhibitory input from GPi. In further support of this idea, we found a significant inverse correlation between left thalamus and left primary motor cortex in all PD subjects ($n = 32$; $r = -0.39$, $P < 0.014$, one-tailed), as predicted.

Another way to address these hypotheses is to examine the thalamic response to levodopa in DID patients before and after pallidotomy surgery. If the thalamic response to levodopa is due to alteration in GPi firing, pallidotomy should reduce the augmented thalamic blood flow response. Such a finding would indicate that the increased thalamic response in DID patients is mediated via output from the basal ganglia rather than direct cortical-thalamic input. Thus, the results of this present study provide a basis for generating specific hypotheses about the mechanisms of DID and the mechanisms by which pallidotomy reduces DID.

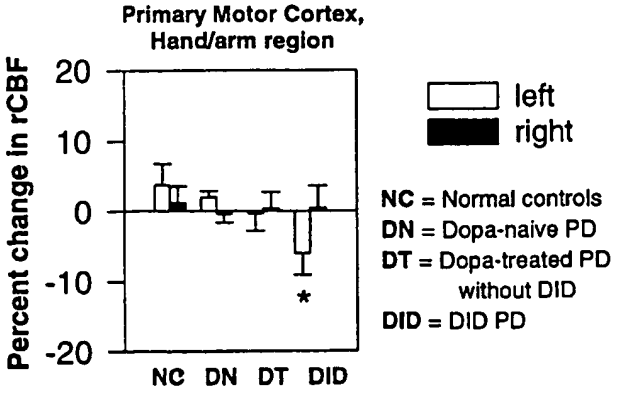

FIG. 3. Mean (± SD) change in blood flow after levodopa administration for left and right primary motor cortex (hand/arm region) for each group. *, Significant difference compared with normal controls and dopa-naïve PD patients.

CONCLUSIONS

In conclusion, we found significantly greater thalamic response to levodopa in PD patients with DID than in PD patients without DID or normals. This difference raises substantial questions about our understanding of how DID are mediated in the brain. Our findings are not consistent with the prevailing hypothesis that DID are mediated by decreased inhibitory output from GPi to thalamus after levodopa administration. However, our results are consistent with the finding that pallidotomy typically reduces DID (3), which is not easily explained by current theory. We hypothesize that levodopa produces elevated blood flow response in the thalamus in patients with DID and that this reflects an alteration in function of neurons projecting from GPi to thalamus. This hypothesis may be tested by comparing dopa-induced blood flow responses in the thalamus of patients with DID before and after pallidotomy. The results of such a test may help to explain the clinical response to pallidotomy.

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